



Research Article

Assessment of Meteorin-like Protein Serum Levels in Pre-diabetes and Newly Diagnosed Type 2 Diabetes Mellitus

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ABSTRACT

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Background: Meteorin-like, is an innovative adipokine, that exhibits elevated expression within adipose tissue and confers advantageous effects upon energy metabolism. Nevertheless, current research pertaining to circulating Meteorin-like levels in obesity remains limited and incongruent. Thus, the objective of this study was to assess Metrnl serum concentrations among adult individuals with pre-diabetes and newly diagnosed type 2 diabetes mellitus and examine its correlation with glucose, HbA1C, and lipid metabolism.

Subjects and Methods: The case-control study incorporated 120 subjects, who were then segregated into three distinct groups, namely control (n = 60), pre-diabetes (n = 30), and newly diagnosed type 2 diabetes mellitus patient's (n = 30). The quantification of serum Meteorin-like concentrations was undertaken by employing an enzyme-linked immunosorbent assay.

Results: The data of the current study demonstrates a significant increase in the concentration of Meteorin-like protein in individuals with newly diagnosed type 2 diabetes mellitus patients as compared to those without the condition ($p \leq 0.001$). A positive correlation between METRNL and various metabolic parameters, such as BMI, FBS, HbA1C, TC, TG, and LDL-C, was observed using the Pearson correlation coefficient. Conversely, a negative correlation was observed between METRNL and HDL-C as well as VLDL-C.

Conclusions: The present study has revealed that serum Meteorin-like levels were found to be elevated in both individuals having newly diagnosed type 2 diabetes mellitus patients and pre-diabetes. Furthermore, the association between serum Meteorin-like levels and lipid profile was observed to be dependent. These findings strongly suggest that the modification of circulating Meteorin-like levels may serve as a promising biomarker for the prognosis of type 2 diabetes mellitus.

Introduction

Diabetes is a metabolic condition causing excessive glucose levels, affecting various body parts, and affecting autoimmune,

metabolic, and genetic illnesses with a common feature: hyperglycemia (1). Diabetes mellitus has increased by over twofold

in the previous thirty years and it is currently the ninth largest reason for death worldwide. Diabetes mellitus affects approximately one out of every eleven people worldwide, with type 2 diabetes making up 90% of occurrences (T2DM) (2). Moreover, the International Diabetes Federation (IDF) predicts that 1.1 million children and adolescents between the ages of 14 and 19 have T1DM (3).

The number of people with diabetes worldwide is expected to increase from 425 million in 2017 to 629 million in 2045. This is due to rising obesity rates and unhealthy habits, influenced by socioeconomic factors like nutrition shifts(4). Type 2 diabetes is becoming increasingly common in teenagers and young adults. Obesity, family history, and a sedentary lifestyle are all important indicators of vulnerability for diabetes type 2, just as they are for type 1 diabetes(5). Type 1 and type 2 diabetes patients experience symptoms like polydipsia, hunger, and urine loss due to insulin insufficiency and hyperglycemia. These symptoms result from improper glucose transport, leading to high blood glucose levels, elevated urine glucose, and calorie and fluid losses(6). Insulin resistance is characterized as a reduced metabolic sensitivity of particular tissues to insulin stimuli, particularly the liver, muscle, and adipose tissue(7). Insulin resistance can be caused by plasma insulin's failure to connect to its receptor or by the existence of a post-receptor binding problem(8)

Pre-diabetes is a condition that occurs before the onset of diabetes mellitus and is characterized by increased glucose levels that are higher than normal but lower than the renal threshold for diabetes (180 mg/dl). This includes impaired fasting glucose (IFG) (6.1-7.0 mmol/L) and impaired glucose tolerance (IGT) after a glucose load (7.8-11 mmol/L), as well as HbA1c levels in the range of 5.7%-6.4% in both states. Pre-diabetes is associated with insulin resistance that occurs before any changes in glucose levels. Annually, 10-15% of people with pre-diabetes progress to type 2 diabetes, with up to 70% eventually getting diabetes (9, 10).

Meteorin-Like protein (METRNL) is a newly discovered secreted protein in white adipose tissue, regulated by insulin sensitivity and encoding the METRNL gene(11). Meteorin-like protein impacts adipose tissue energy consumption and inflammation, found in various tissues and organs.(12). Metrnl, initially an adipokine with pleiotropic effects on glucose homeostasis, may have protective functions in cardiometabolic and inflammatory disorders. Physiological activities, like exercise, temperature changes, and high-fat meals, may influence Metrnl expression(13). Exercise training boosts energy expenditure and combats obesity and metabolic issues(14). Metrnl activates the AMP-activated protein kinase (AMPK) pathway, promoting glucose uptake and fatty acid oxidation in skeletal muscle and adipose tissue, maintaining cellular energy homeostasis(15).

Subjects and Methods

Collection and Preparation of Samples

This study's case-control design, the study included 120 individuals from Iraq. Among them, 30 had prediabetes, 30 had newly diagnosed type 2 diabetes mellitus patients, and 60 were in good health and served as the control group. There were 68 males and 52 females, and their ages ranged from 31 to 65 years. The study was

conducted at the Chemistry and Biochemistry Department of Al-Imamin Al-kadmeen Medical City. Participants were examined by a physician and were interviewed in a well-structured manner. Height, weight, and BMI measurements were taken during the physical exam. A blood samples were collected from participants when they were fasting during their visit. The diagnoses of prediabetes and T2DM were made in accordance with the American Diabetes Association's (ADA) recommendations. (1).

Inclusion criteria:

group 1 (control) 60 blood samples from healthy volunteers who match the patient's age and sex for type 2 diabetes and pre-diabetes but have no prior history of the condition will be taken.

group 2 (pre-diabetes) 30 patients with pre-diabetes, who have FBS 100-125 mg/dL(5.6 – 6.99 mmol/L), (HbA1C > 5.7% or <6.5%), will have blood samples taken.

group 3 (newly diagnosed 2 diabetes mellitus) Thirty individuals who have newly diagnosed type 2 diabetes mellitus, FBS \geq 126 mg/dL(7.0 mmol/L), (HbA1C > 6.5%).

Exclusion criteria:

Pregnant women and chronic renal failure will be excluded from this study's eligibility criteria. Diseases of the liver, thyroid, Type 1 diabetes, cardiovascular disease, diabetic renal disease, rheumatoid arthritis, and those who have recently taken statins and NSAIDs.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Al-Nahrain University \ College of Medicine Affiliated to Al-Imamin Al-kadmeen Medical Cit. The patients/participants provided their written informed consent to participate in this study.

Biochemical measurements

standardized protocols were used to measure height and body weight. To calculate Body Mass Index (BMI), we divided weight by height squared (kg/m²). Eight milliliters of blood were drawn from both patients and controls, and the results were as follows:

1. For the HBA1c test, two milliliters of blood will be drawn and placed in EDTA tubes.
2. Six milliliters of blood will be drawn into a gel tube and left at room temperature for 20 minutes. Following coagulation, the blood samples will be separated by centrifugation for 10 minutes and divided into small amounts for measurements of
 - a. Fasting blood sugar and lipid profile by enzymatic and colorimetric method.
 - b. serum Meteorin-Like protein. It will be determined by using enzyme-linked immuno- sorbent assay (ELISA) kit (Sunlong/China).

Statistical analysis

To analyze the data, SPSS version 26 and Microsoft Excel 2019 were utilized. To determine the cutoff value, specificity, and sensitivity of METRNL, the receiver operator characteristic curve (ROC) was utilized. Numerical data was described using Mean \pm SD. The levels of serum METRNL were correlated with exogenous factors

such as age, gender, and body mass index (BMI). The Student's t test was used to determine the individual p-value between control and patients groups, while the Student's F test (ANOVA) was used to determine the individual p-value of different groups between control, pre-DM, and T2DM. A significance level of $p < 0.05$ was deemed significant. The correlation coefficient (r) measures how closely two variables are related, with a range between (-1-1). A positive correlation is represented by an r range from 0 to 1, while a range from -1 to 0 represents a negative correlation. Person correlations r above 0.4 are typically considered a strong correlation, while Person correlations r between 0.2 and 0.4 are regarded as moderate, and correlations less than 0.2 are deemed poor.

Results

Characteristic of the study population

The clinical features pertaining to the study cohort are depicted in Table 1. The participants were divided into three groups, pre-diabetes, newly diagnosed type2 diabetes mellitus and normoglycemic subjects. There were no statistically significant differences in age and sex among the study groups. Compared with normal group. Participants with prediabetes and newly diagnosed type2 diabetes mellitus have higher level of BMI, FBS, HbA1c, T.C, TG, VLDL-C, LDL-C and meteorin-like protein as shown in Table 1 and figure 1. While, lower levels of HDL-C. However, there were a highly significant difference in METRNL, FBS, HbA1C, T.C, TG, HDL-C, LDL-C, VLDL-C between the three groups(all $p < 0.001$).

Table1 Clinical and biochemical characteristics of all the study participants

Parameter	Control	Pre-diabetes	Type2DM	P
	N= 60	N= 30	N=30	
Age (years)	44.30±10.21	46.73±11.24	48.34±10.39	0.079
METRNL(ng/ml)	6.26±1.31	8.18±1.64	11.08±2.5	< 0.001
FBS (mg/dl)	89.74±11.74	118.76±12.47	176.68±19.2	< 0.001
HbA1C (%)	5.24±0.30	6.17±0.27	8.22±1.17	< 0.001
BMI (Kg/m ²)	26.89±4.23	27.52±4.36	30.58±3.95	< 0.001
Cholesterol(mg/dl)	180.06±31.23	195.8±28.53	210.13±30.74	< 0.001
Triglyceride(mg/dl)	108.91±33.04	139.91±29.82	172.66±36.93	< 0.001
HDL(mg/dl)	45.39±6.45	38.49±6.02	40.29±8.49	0.004
LDL(mg/dl)	94.72±18.92	103.7±15.87	116.21±32.47	< 0.001
VLDL (mg/dl)	31.73±12	38.18±7.11	45.88±12.47	< 0.001

n: number of cases; data were presented as mean and standard deviation; P: One way ANOVA; Post hoc Tukey's test; **: highly significant at $P \leq 0.01$; *: significant at $P \leq 0.05$; P1: Control vs. pre-diabetic; P2: Control vs. DM; P3: Pre-diabetic vs. DM

Correlation between serum METRNL levels and with clinical and laboratory parameters:

The subsequent stage in this research endeavor entails approximating the association between serum METRNL levels and various parameters in all population subgroups by employing person correlation coefficients analysis (as presented in Table 2). Serum METRNL demonstrated a positive and significant correlation with BMI ($P = 0.012$, $r = 0.264$), FBS ($P = 0.042$, $r = 0.204$), HbA1C ($P = 0.001$, $r = 0.689$), total cholesterol ($P = 0.013$, $r = 0.260$), Triglyceride ($P = 0.003$, $r = 0.308$), LDL($P = 0.020$, $r =$

0.246). and was negatively associated but statistically not significant with HDL($P = 0.135$, $r = -0.159$ and VLDL-C ($P = 0.619$, $r = -0.053$). As a result of the extremely significant difference in METRNL levels between newly diagnosed diabetes patients and pre-diabetes groups, a receiver operator characteristic (ROC) curve analysis was performed, and the findings were as follows: the cut off value was >8.37 ng/mL, with an AUC 91.6, sensitivity of 96.7%, and specificity of 80.0%.

Table 2: the correlation between METRNL and the clinical and laboratory parameters.

Parameter	(METRNL)	
	P	r
BMI (kg/m ²)	0.012 *	0.264
FBS (mg/dl)	0.042 *	0.204
HbA1C (%)	<0.001**	0.689
Total Cholesterol (mg/dl)	0.013 *	0.260
Triglyceride (mg/dl)	0.003 **	0.308
LDL (mg/dl)	0.020 *	0.246
HDL (mg/dl)	0.135	-0.159
VLDL (mg/dl)	0.619	-0.053

* Significant difference $P < 0.05$.

By using Pearson correlation coefficient test. P value < 0.05 was regarded as significant, and the correlation coefficient (r), which measures how closely two variables are related, has a range between (-1-1); the r range from 0 to 1 represents positive correlation, and negative correlation to the r range from -1 to 0.

Table 3 ROC and cutoff value of METRNL in studied groups.

marker	Cutoff value	AUC	Accuracy	P	Sensitivity	Specificity
METRNL	8.37 ng/mL	91.6%	85.5%	0.000	96.7%	80.0%

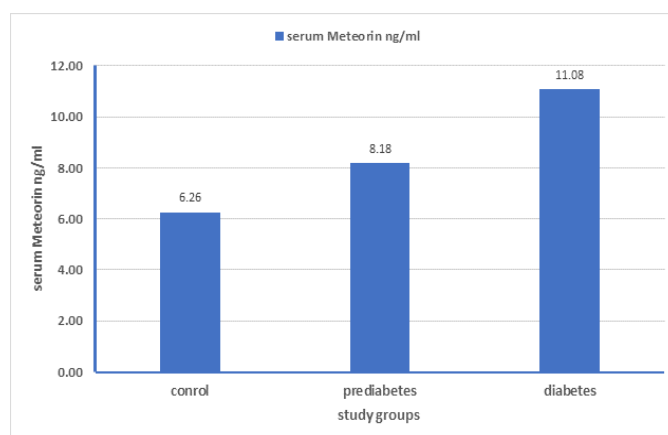


Figure 1. METRNL serum level in each study group.

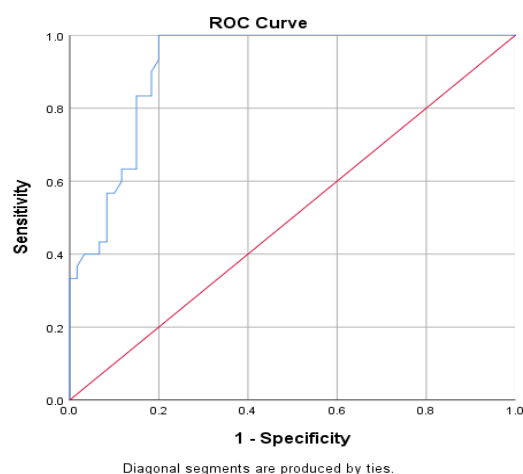


Figure 2: ROC and cutoff value of METRNL in the study population

Discussion

Adipokines play a crucial role in maintaining the metabolic homeostasis of the entire body via intra- and inter-tissue communication. Nonetheless, the dysregulated biosynthesis and secretion of these hormones (adipokines) in certain pathological conditions, especially obesity, can lead to the onset of diverse metabolic disorders. The significance of adipokines is thus evident and their intricate functioning necessitates further research into their underlying mechanisms to devise effective therapeutic interventions. In this particular investigation, it was observed that the concentrations of serum Metrn1 were found to be increased in subjects who were diagnosed with newly diagnosed type 2 diabetes mellitus and pre-diabetes mellitus when compared to individuals who were in good health. A more noteworthy observation was that elevated levels of Metrn1 were found to be closely associated with the lipid profile. The results of this study suggest that Metrn1 could be a promising biomarker for the early diagnosis of type 2 diabetes mellitus. It is, therefore, imperative to further investigate the potential role of Metrn1 in the pathogenesis of diabetes mellitus.

Meteorin-like protein (METRNL), also referred to as Meteorin- β , interleukin-41 and subfatin, has recently emerged as a hormone with significant implications in metabolic regulation and is being considered as a potential biomarker for metabolic syndrome. Subsequent investigations have demonstrated that peroxisome proliferator-activated receptor- γ (PPAR γ) plays a role in augmenting the capacity of METRNL to counteract insulin resistance in adipose tissue. This finding underscores the potential therapeutic value of METRNL in treating metabolic disorders (16). Despite numerous studies investigating the association between Metrn1 levels in circulation and T2DM, the current findings suggest that Metrn1 could play a crucial role in the pathophysiological processes of metabolic diseases, including T2DM. Previous studies have reported varying results on the serum levels of Metrn1 in T2DM patients, indicating a need for more research in this area. For instance, some studies, such as those by Lee et al. (11) and Zheng et al. (17), found lower serum levels of Metrn1 in newly diagnosed T2DM patients. Conversely, other studies, such as that by Chung et al. (18), reported increased

serum levels of Metrn1 in T2DM patients. These discrepancies in findings suggest that there may be other factors influencing the relationship between Metrn1 and T2DM, which requires more comprehensive analysis. Further research could help elucidate the molecular mechanisms underlying the role of Metrn1 in T2DM and other metabolic diseases. Such findings could have significant implications for the development of novel therapeutic approaches for these conditions. In addition, it could also help to identify biomarkers that could aid in the early diagnosis and management of metabolic diseases, such as T2DM. Thus, it is essential to continue exploring the role of Metrn1 in metabolic diseases through rigorous scientific investigation. Studies conducted previously have demonstrated a correlation between obesity and reduced levels of Metrn1 in the bloodstream (19-21).

Conclusion

A study found that patients newly diagnosed with type 2 diabetes mellitus (T2DM) and pre-diabetes mellitus had higher levels of the protein meteorin-like (Metrn1) in their blood. These levels were linked to changes in their lipid and glucose profiles, and were able to accurately distinguish between prediabetes and T2DM.

Recommendations

Studies need to expand the pool of participants from various centers for the METRNL trial involving patients with prediabetes and type 2 diabetes. Further investigation is needed to evaluate the levels of oxidative stress markers, specifically superoxide dismutase (SOD) and reactive oxygen species (ROS), in the blood of individuals with pre-diabetes or newly diagnosed type 2 diabetes.

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Compliance with ethical standards

The author declares the absence of any conflicts of interest

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Conflict of Interest

Authors declare no conflict of interest.

Data availability

Data are available upon reasonable request.

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